REMARKS

The above-identified application was filed as a continuation application based on US Patent Application 09/261,104 filed March 3, 1999, now US Patent 6,630,140.

In the August 27, 2002 Official Action in the '104 Application, the Examiner rejected claims 3, 9-11, 19-20, 28, and 30-42 under 35 U.S.C. §103(a) as allegedly being unpatentable over Fick et al. (WO 9704807) in view of Platz et al. (US 6,019,968, filed 4/14/1995) and Jager et al. (US 5,676,930). Claims 4 and 14 were also allegedly unpatentable over Fick et al. (WO 9704807) in view of Platz et al. (US 6,019,968, filed 4/14/1995) and Jager et al. (US 5,676,930) and further in view of Bonnefoy et al. (WO 9612741).

In accordance with the present amendment, claim 1 has been amended to recite a method for preventing induction of an asthmatic state in a human by administering an agent that selectively inhibits binding of IgE to an anti-FcεRII receptor protein present on airway smooth muscle cells thereby preventing induction of said asthmatic state in said human. Claims 14 and 30 have also been amended accordingly. As a result of the foregoing amendments to claims 1, 14, and 30, it is respectfully submitted that the presently claimed methods are patentably distinct from the methods of Fick et al. as combined with Jager et al., Platz et al. or Bonnefoy et al.

The above-noted rejections based on 35 U.S.C. §103, as set forth in the August 27, 2003 Official Action in the '104 Application, which presumably will be repeated in the first Official Action in the present application, are respectfully traversed.

Before addressing the merits of the anticipated §103 rejection, a brief overview of the methods of the invention is set forth below.

As discovered by the present inventors and set forth in the above-identified applications, airway smooth muscle cells

(ASM) express the inducible, low-affinity FcεRII receptor (also known as CD23). Notably, while the FcεRI receptor (the high-affinity receptor) is present on Mast cells, ASM do not express this receptor.

In the immediate reaction of asthma, there is IgE-mediated activation of the FcεRI (or high-affinity receptor) on mast cells and this leads to degranulation and release of inflammatory molecules thought to be important in asthma. Others have noted that expression of CD23 is upregulated in some cells from asthmatic patients, specifically bone marrow-derived cells including monocytes, alveolar macrophages, and B lymphocytes. The present inventors are the first to determine which Fcε receptors were present on ASM.

It had previously been appreciated that exposure of isolated human ASM to atopic asthmatic serum induces release of cytokines, but the molecular mechanism underlying this reaction was unknown. The results presented in the specification show unequivocally that the enhanced restrictor/attenuated relaxor responses of ASM (characteristic of the asthmatic response) are due to the interaction of IgE with CD23. This statement is supported by the following observations:

- The response is blocked in the presence of a monoclonal Ab to CD23.
- Removing the immunoglobulins (IgE) from the serum abrogates the response.
- CD23 mRNA is induced following stimulation of ASM by atopic asthmatic serum.
- CD23 protein expression is also increased following exposure to atopic asthmatic serum.
- CD23 protein expression is also upregulated in ASM's of asthmatic patients (see Hakonarson et al., (Sept. 1999) J. Allergy Clin. Immunol., 575-

584, which is the work of the instant inventors, and is included herewith.)

- The response is specific to CD23 as another IgE receptor (FcγRIII) present on ASM is not induced by atopic asthmatic serum.

THE PRESENT CLAIMS ARE NOT RENDERED OBVIOUS BY THE DISCLOSURES IN FICK ET AL., PLATZ ET AL., JAGER ET AL., OR BONNEFOY ET AL.

As noted by the PTO Board of Appeals in Ex parte Wolters, 214 U.S.P.Q. 735 (Bd. Apps. 1979), the burden of establishing *prima facie* case of obviousness falls upon the Examiner. In determining whether a case of *prima facie* obviousness exists, it is necessary to ascertain whether or not the disclosure of the cited prior art would appear to be sufficient to one of ordinary skill in the art to make the claimed substitution, combination or other modification. In re Lalu, 223 U.S.P.Q. 1257 (Fed. Cir. 1984). Merely because it is possible to find several prior art disclosures which might be combined to arrive at the claimed subject matter does not make the combination of the disclosures obvious, unless the art also contains something to suggest the desirability of the proposed combination. In re Imperato, 179 U.S.P.Q. 730 (CCPA 1773).

Finally as set forth in MPEP §2141.03, Obviousness cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established. In re Rijckaert 9 F.2d 1531, 28 USPQ 2d 1995.

Inasmuch as Fick et al. were unaware that 1. There are several types of IgE receptors present in the human body; 2. the low affinity IgE receptor present on airway smooth muscle cells mediates the increased contraction and decreased relaxation of airway tissue and 3. teach methods of "sopping up" all circulating IgE for treating asthma, it cannot be reasonably maintained that the subject matter of amended claim 1 is rendered obvious by the teaching of Fick et al. These

above-noted deficiencies of Fick et al. are not overcome by combining Fick with either Jaeger, Platz, or Bonnefoy.

In the instant case, no motivation exists to combine the teachings of Fick et al. with those of Platz et al. and Jager et al. Fick et al. teach the use of IgE antagonists for binding soluble IgE thereby removing it from circulation or, in the alternative, blocking the binding of IgE to its receptors that reside on **bone marrow-derived** cells. However, as stated above, Fick et al. did not appreciate that FcεRII is present on ASM cells and that the enhanced restrictor/ attenuated relaxor responses of ASM (characteristic of the asthmatic response) are due to the interaction of IgE with FcεRII on these particular cells. The IgE antagonists disclosed by Fick et al. are expected to exhibit their function of inhibiting asthmatic responses by systemically complexing free IgE or blocking the binding of IgE to its receptors present on **bone-marrow derived cells**. Inasmuch as Fick et al. were unaware that elevated expression of FcεRII on ASM cells is directly responsible for the manifestation of the pro-asthmatic phenotype, it would NOT be obvious to administer an agent that selectively targets this particular FcE receptor which resides on airway smooth muscle cells. Further, it is arguable that Fick et al. teach away from the present claimed methods as the IgE antagonists disclosed do not differentiate the different types of IgE receptors. The disclosure of "IgE receptors" would include FcεRI and CD23 (FcεRII). These receptors are very different with respect to their molecular structure and characteristics of binding to IgE, and differ in their known physiological functions. FcεRI belongs to the immunoglobulin superfamily and is similar in sequence and structure to the immunoglobulin G Fc receptors, whereas CD23 belongs to the C-type lectin superfamily of proteins. Pharmacologically, FcεRI binds to the Fc region of IgE with very high affinity (Ka approximately 10^{-10} M^{-1}), where CD23 binds IgE with much lower affinity (Ka approximately 10^{-7} M^{-1}).

FcεRI is characteristically expressed on mast cells and basophils where its activation, triggered by IgE/FcεRI complexed to allergen, triggers the release of various mediators (e.g. histamine, leukotrienes, cytokines) that are implicated in the immediate inflammatory response. FcεRI has also been found on monocytes, Langerhans cells and dendritic cells where it is involved in antigen presentation, and on eosinophils where it plays a role in host defense against parasitic infections.

CD23 or FcεRII is also expressed on a variety of cell types. These include antigen-presenting cells, and its activation has been associated with regulation of IgE production and antigen presentation by B-lymphocytes. Unlike FcεRI, cellular activation by CD23 has been attributed to its interaction with other cell surface-bound molecules including complement receptor (CR)-2, as well as CR3 and CR4, both of which are members of the integrin superfamily of molecules that have been implicated in inflammatory processes. Thus, the two receptors have distinct molecular and biochemical functions.

Additionally, even if the teachings of Fick et al., Platz et al., and Jager et al. were to be combined, the methods of treating asthma as recited in the present claims are unexpectedly superior to methods of treating asthma by administering the IgE antagonists, as disclosed in the prior art. It has been stated by the Federal Circuit:

> One way for a patent application to rebut a *prima facie* case of obviousness is to make a showing of "unexpected results," i.e., to show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected. The basic principle behind this rule is straightforward--that which would have been surprising to a person of ordinary skill in a particular art would not have been obvious. The principle applies most often to the less predictable fields, such as chemistry, where minor changes in a product or process may yield substantially different

results.

In the instant case, the methods taught by Fick et al. target free IgE in circulation, therefore interfering with the normal immune protective functions of IgE in general and compromising the long-term immune status of the patient. The methods recited by the present claims selectively target FcεRII on ASM cells and thus control the bronchial tissue response to IgE rather than eliminating IgE altogether. This method therefore is superior, as it specifically targets binding to the low affinity IgE receptor, and therefore avoids the potential detrimental effects of removing free IgE from circulation.

Finally, Applicants respectfully submit that Fick et al. and Platz et al. are not properly citable against this application. Under the Patent and Trademark rules of practice, when any claim of a U.S. patent application is rejected on reference to a printed publication, the timely filing of a Declaration showing conception of the invention prior to the effective date of the reference and subsequent diligent reduction to practice in this country, will remove the publication as a bar to the grant of a patent to the inventor.

Pursuant to 37 C.F.R. §1.131, the Declaration of Drs. Grunstein and Hakonarson filed in the '104 application, clearly establishes conception of the claimed subject matter of the present application which predates the April 14, 1995 filing date of Platz et al. (Fick was filed July 27, 1995) and subsequent diligent reduction to practice. It is believed that this Declaration provides evidence which overcomes the §103(a) rejection of the present claims based upon Fick et al., Platz et al., and Jager et al. The Examiner is requested to consider this declaration, in accordance with MPEP 201.06(c). A copy of the declaration is enclosed. Accordingly, withdrawal of the §103(a) rejection is

respectfully requested.

Regarding the inclusion of Bonnefoy to support a potential §103 rejection, Applicants respectfully submit that again, no *prima facie* case of obviousness can be made out based on the references relied on by the Examiner. As discussed above, there is neither suggestion nor motivation to combine Fick et al., Platz et al., and Jager et al. Bonnefoy, who teaches the use of anti-FcεRII receptor protein antibody for treating arthritis in mice fails to make up for the deficiencies of the combination of Fick, Platz and Jager. Bonnefoy teaches that FcεRII is expressed on haematopoietic cells. Bonnefoy is silent regarding the expression of FcεRII on ASM cells and also fails to recognize that elevated expression of FcεRII expression on ASM cells manifests the asthmatic reaction. Accordingly, there is no suggestion or motivation in combining the teachings of Bonnefoy et al., Platz et al., and Jager et al. in method of administering anti-FcεRII receptor protein antibodies to selectively block this receptor on ASM cells to treat asthma.

Additionally, as indicated above with the previous §103 rejection, Fick et al. and Platz et al. are not properly citable against this application as evidenced by the 37 C.F.R. §1.131 Declaration of Drs. Grunstein and Hakonarson submitted herewith.

Favorable consideration leading to prompt allowance of the present application is respectfully requested.

Respectfully submitted,
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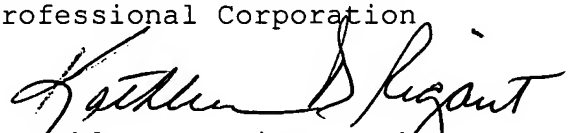
By 
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Enclosures: Manuscript by Grunstein et al. and copy of previously filed Rule 131 Declaration